The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 19

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte NORMAN TERRY, ELIZABETH PILON-SMITS, and YONG LIANG ZHU

MAILED
JUL 31 2003
U.S. PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Appeal No. 2002-0252
Application No. 09/365,349

ON BRIEF

Before WILLIAM F. SMITH, ADAMS, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-24. In the Examiner's Answer, the examiner stated that claims 4, 9-12, 16-18, 21, 23 and 24 were inadvertently included in the rejection of October 24, 2000, thus claims 1-3, 5-8, 13-15, 19-20 and 22 are the subject of this appeal. It is thus our understanding that it is examiner's position that claims 4, 9-12, 16-18, 21, 23 and 24 are free of any rejection. Moreover, in deciding this appeal, we have also considered the record in related Appeal No. 2002-0254, Application No. 09/365,348.

Claims 1, 3 and 8 are representative of the subject matter on appeal, and read as follows:

1. A plant which is genetically engineered to overexpress glutamylcysteine synthetase and thereby provides enhanced heavy metal accumulation as compared with a corresponding wild type plant.

3. A plant according to claim 1 which is a member of the brassicaceae family.

8. A plant according to claim 1, wherein the enhanced accumulation is at least 50% greater than an otherwise comparable untransformed plant.

The examiner relies upon the following references:

De Knecht et al. (De Knecht) "Evidence against a role for Phytochelatins in Naturally Selected Increased Cadmium Tolerance in Siliene Vulgaris (Moench) Garcke," New Phytol., Vol. 122, pp. 681-688 pp. 685-687 (1992)

Delhaize et al. (Delhaize) "Poly (gamma-glytamylcysteinyl)glycine Synthesis in Datura Innoxia and Binding with Cadmim: Role in Cadmium Tolerance," Plant Physiology, Vol. 89, pp. 700-706 (1989)

Noctor et al. (Noctor) "Glutathione: Biosynthesis, Metabolism and Relationship to Stress Tolerance Explored in Transformed Plants," Journal of Experimental Botany, Vol. 49, No. 321, pp. 623-647 (1998)

Goldsbrough "Metal Tolerance in Plants: The Role of Phytochelatins and Metallothioneins," Ann Arbor Press, pp. 221-228 (1999)

Chen et al. (Chen) "Increased Activity of Gamma-Glutamylcysteine Synthetase in Tomato Cells Selected for Cadmim Tolerance," Plant Physiology, Vol. 106 pp. 233-239 (1994)

Arisi et al. (Arisi) "Modification of Thiol Contents in Poplars (Populus tremula X P. alba) Overexpressing Enzymes Involved in Glutahione Synthesis," Planta, Vol. 203 pp. 362-372 (1997)

Claims 1-3, 5-8, 13-15, 19-20 and 22 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. After careful review of the record and consideration of the issues before us, we affirm the rejection as to claims 1, 2, 5-8, 13-15, 19-20 and 22, but reverse the rejection as to claim 3.

BACKGROUND

The invention relates to phytoremediation, wherein plants are used to remove heavy metals by sequestering, stabilizing or biochemically transforming them. One such plant that is useful in phytoremediation is a hyperaccumulator: A hyperaccumalator is a plant that accumulates heavy metals from metal-containing sites. See Specification, page 1.

According to the specification:

> Non-protein thiols (NPTs), which contain a high percentage of cysteine sulfhydryl residues in plants, play a pivotal role in heavy metal detoxification. Glutathione (γ-Glu-Cys-Gly, GSH) is one of the most important components of NPT metabolism. . . . Glutathione is synthesized from its constituent amino acids in two sequential, ATP-dependent enzymatic reactions, catalyzed by γ-glutamyl-cysteine synthetase (ECS) and glutathione synthetase (GS), respectively.

Id. at 1-2 (citations omitted).

The invention relates to

> methods and compositions for heavy metal phytoremediation. The subject compositions include plants which are genetically engineered to overexpress glutamylysteine synthetase and thereby provide enhanced heavy metal accumulation. In particular embodiments, the plants comprise a gene encoding ECS operably linked to a heterologous promoter, the plant is a member of the Brassicaceae family, such as Brassica juncea, and/or the heavy metal is cadmium.

Id. at 3.

According to the specification, "[s]uitable plants are readily screened for requisite engineeribility and expression," and the specification presents a laundry list of plants. See id. at 4-6. In an exemplary embodiment, Brassica juncea plants were transformed with an ECS construct that was described in the prior art by Arisi. The construct contains the E. coli gshI gene, fused to a pea chloroplast transit sequence and driven by a double-enhanced 35S CaMV promoter. See id. at 8.

DISCUSSION

Claims 1-3, 5-8, 13-15, 19, 20 and 22 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification fails to enable the full scope of the claimed subject matter. We affirm the scope of enablement rejection as to claims 1, 2, 5-8, 13-15, 19, 20 and 22, but reverse as to claim 3.

As an initial matter, we acknowledge appellant's letter received June 2, 2003 in related Appeal No. 2002-0253, Application No. 09/365, 349. In that letter, appellants state that an identical continuing application to the 09/365,349

application was filed, which application was issued on June 10, 2003 as U.S. Patent No. 6,576,816. Issued claim 1 reads as:

> 1. A Brassica plant which is genetically engineered to overexpress glutamylcysteine synthetase and thereby provides enhanced heavy metal accumulation as compared with a corresponding wild type plant.

The above issued claim is very similar to claim 1 that is the subject of these appeal, except that it is limited to a Brassica plant. Given the allowed claim, we reverse the rejection as to instant claim 3, as claim 3 specifies that the genetically engineered plant is a member of the brassicacae family. Moreover, in view of the examiner's allowance of the above claim in the continuation application of the instant application, we limit our review of the scope of enablement rejection to how it pertains to plant species other than Brassica.

We also note appellants statement that claims 5, 7 and 14, claim 6, and claim 19 do not stand or fall with claim 1. See Supplemental Brief on Appeal, pages 3-4. But because we are limiting our analysis as noted above, and because those claims are not limited to Brassica plants, we also affirm the scope of enablement rejection with respect to those claims.

According to the rejection,

> the specification, while being enabling for transformed Brassica juncea overexpressing a glutamylcysteine synthetase (ECS) for an improved tolerance to selected heavy metals, does not reasonably provide enablement for any transformed plant capable of enhancing accumulation of a wide variety of heavy metals by overexpressing an ECS, and a method for decreasing heavy metal content of a medium by growing said plant. The specification does not enable any person skilled in the art to which it pertains, or with

> which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Examiner's Answer, page 6.

The rejection asserts that "the specification provides guidance only for the transformation of Brassica juncea with the ECS gene from E. coli driven by double-enhanced 35S CaMV promoter, and wherein the analysis of heavy metal tolerance involves only hydroponic or agar medium with Cd concentrations of 0.15-0.25 mM of CdSO4." Id. While the rejection acknowledges that a table in the specification states that the ECS gene was introduced into other plant species, it states that "it is unclear how these results were obtained, especially the '+++' for every transgenic species and '+/-' for every corresponding wild-type plant." The rejection further notes that no data was presented to support the results presented by the table, and that it is unclear how the "+++" corresponds to the "at least 50%" enhanced heavy metal accumulation as compared to wild-type. Id. at 7.

The examiner relies upon Noctor, as well as Goldsbrough, De Knecht, Chen and Dehaize to demonstrate that it would require an undue amount of experimentation by one skilled in the art to practice the full scope of the claimed invention. With respect to Noctor specifically, the examiner notes that the reference teaches that overexpession of an ECS enzyme in poplars did not increase Cd tolerance in transgenic poplars grown in Cd contaminated soil. Id. at 7-8.

"[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original). "[It] is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." Id. at 224, 169 USPQ at 370. The examiner, however, has provided objective evidence, in the form of Arisi and Noctor, that the specification fails to enable the full scope of the claims, and thus it would require an undue amount of experimentation by one skilled in the art to practice the claimed invention with plants other than Brassica plants.

As noted by the examiner, appellants provide a table on pages 7 to 8 of the specification setting forth exemplary plant species demonstrating enhanced heavy metal accumulation in wild-type plants and the corresponding plant overexpressing recombinant glutamylcysteine synthetase. Each wild-type plant received a "+/-", and each recombinant plant received a "+++". No data is

presented in the specification in support of the table, nor does the specification define what amounts correspond the "+/-" and "+++" designations.

The specification provides a single example of transformation of Brassica juncea (Indian mustard seeds), along with the supporting data. See Specification, pages 8-12. According to the specification,

> The ECS gene construct used was described earlier by Arisi et al. (1997). It contains the E. coli gshI gene, fused to pea chloroplast transit sequence and driven by the double-enhanced 35S CaMV promoter.

Id. at 8.

Arisi, which is the same reference cited in the above passage from the specification, teaches transformation of a hybrid poplar with the E. coli gene for glutamylcysteine synthase gene, resulting in a poplar that overexpresses the ECS gene. See, e.g., Arisi, page 369. As also noted above, the construct taught by Arisi is the same construct used to generate the hyper-accumulating Brassica plants exemplified by the specification. As taught by Noctor, however, the hybrid poplar plants of Arisi are not hyper-accumulators. According to Noctor,

> Poplar overexpressing [ECS] presents an excellent model system in which to investigate the roles of this enzyme . . . in phytochelatin-mediated resistance to heavy metals. In preliminary experiments, transformants overexpressing [ECS] in the cytosol . . . were exposed for 14 d to different Cd. Concentrations (0-1000$\mu g\ g^{-1}$ soil). In transformed and untransformed poplars, Cd accumulated to a similar extent.

Noctor, page 640, col. 1.

Moreover, with respect to the hybrid poplars of Arisi that overexpress the ECS enzyme, appellants have stated on the record, citing Noctor, that the genetically engineered poplars produced by Arisi do not demonstrate increased heavy metal accumulation when compared to wild-type. See Appeal Brief, page 3. Appellants specifically noted that:

> The prior art establishes an uncertain and unpredictable relationship between ECS expression and heavy metal accumulation, and specifically teaches (in both Noctor [ ] and Goldsbrough) that over expression of ECS will not yield heavy metal accumulators.

Id. at 4-5.

Because, as recognized by appellants, the prior art establishes an uncertain and unpredictable relationship between overexpression of glutamylcysteine synthetase, and because, as discussed above, the specification provides only a single example of a hyperaccumulating plant, it would require an undue amount of experimentation by one skilled in the art to practice the invention using plants other that Brassica plants without further guidance from the inventors of why overexpression of glutamylcysteine synthetase produced hyperaccumulating Brassica plants, but failed to produce hyperaccumulating poplar plants.

Appellants argue that "[t]he claims do not encompass 'any plant' as repeatedly alleged by the Examiner, but rather only a plant structurally limited to a plant genetically engineered to overexpress glutamylcysteine synthetase and functionally limited to one which does in fact overexpress the recited

glutamylcysteine synthetase and thereby provides enhanced accumulation of the targeted heavy metal as compared with a corresponding wild type plant." Supplemental Brief on Appeal, page 4 (emphasis in original). Appellants contend that suitable plants are readily screened for "requisite engineerability," and the specification offers a large number of suitable, commercially available plant source materials. Appellants also asserts that "exemplified plants include Brassica juncea, Populus angustifolia, Nicotiana tabacum and Silene cucubalis. The suitability of any given plant is readily ascertained by simple substitution into the same method." Id. Page 5.

In order to meet the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification need to teach the skilled artisan to make and use the claimed invention. Although appellant asserts that exemplified plants include Brassica juncea, Populus angustifolia, Nicotiana tabacum and Silene cucubalis, as discussed above, the Populus angustifolia, Nicotiana tabacum and Silene cucubalis plants are only presented in a table with heavy metal accumulation represented by the "+/-" and "+++" designations. As also noted above, there is no data presented in the specification to support the results presented by the table. The only example provided by the specification that is supported by a description of the methodology used, as well as supporting data, is the transformation of a Brassica juncea with glutamylcysteine synthetase to provide a plant that demonstrates heavy metal accumulation.

The Noctor reference, however, teaches that a hybrid poplar plant, transformed with the same glutamylcysteine synthetase construct as used in the example, did not result in a plant that provides enhanced heavy metal accumulation as compared with a corresponding wild type plant. Thus, the specification provides an example of a Brassica hyperaccumulator, while the prior art teaches that a poplar transformed with the same construct did not result in a hyperaccumulator. In view of the Noctor reference, and the fact that the specification provides only a single example of a hyperaccumulating plant, wherein the example is supported by a description of the methodology used and the supporting data, it would require an undue amount of experimentation by one skilled in the art to practice the invention using plants other that Brassica plants.

With respect to Noctor, appellants argue that Noctor did not have the benefit of the instant specification, which teaches how to make hyper-accumulating plants, including poplars. Appellants argue further that:

> We do not know how Noctor [ ] did their experiments, so it is not possible for us to determine why they failed: we do not know in what form they provided the Cd, we do not know whether their poplars were subject to other variables that would have interfered with accumulation, we do not know how they made their transformants, we do not know whether their preliminary experiments were based on one or two anomalous plants, we do not know if their soil had other toxins or confounding microorganisms that may have independently depleted the supplemented Cd, etc. It is possible that the results of Noctor [ ] are based on experimental error or contaminated materials. On the other hand, it is possible that they result merely from an insufficient sample size – had they generated sufficient data, they may well have obtained hyper-accumulators. Unless she has secret information about Noctor['s] [ ] work, the Examiner's proposed "only

> reasonable explanation" [ ][1] for Appellants success does not reflect even a basic understanding of the scientific methodology.

Reply Brief on Appeal, page 2.

As noted by the examiner, the specification provided no data to support the results in the table. The specification also did not provide information on how the hyperaccumulating plants, including the poplars, were produced, under what conditions they tested, in what form the Cd was provided, nor the sample size tested. Thus, we are unable to determine from appellants specification why the poplars were presented in the table as hyperaccumulators, and how they differed from the poplars produced by Arisi.

Appellants argue further that the prior art, such as Noctor, demonstrates that simple upregulation of a gene, such as ECS, in response to cultivation of the plant in the presence of a heavy metal, does not suggest that the plant will demonstrate enhanced accumulation. According to appellants:

> The prior art establishes an uncertain and unpredictable relationship between gultamylcysteine synthetase and heavy metal exposure, and specifically teaches (in Noctor [ ] . . .) that overexpression of enzymes upregulated upon heavy metal exposure, including glutamylcysteine synthetase, will not yield heavy metal accumumulators.
>
> This unpredictability relates to extrapolating from gene upregulation to metal accumulation and has no bearing on substituting one plant for another in the claimed methods, wherein enhanced accumulation is demonstrated—in fact, it is

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[1] "The only reasonable explanation for Appellants' apparent success in a single Brassica species, namely Brassica juncea, is that the genetic background of the plant species to be transformed has a strong influence on the ability of the introduced transgene to cause heavy metal overaccumulation or tolerance." Examiner's Answer, page 11.

> demonstrated in a variety of diverse exemplary plants. The specification aptly enables one of ordinary skill in the art to practice the method in any plant which is genetically engineered to overexpress glutamylcycteine synthetase and thereby provide enhanced accumulation of the heavy metal.

Supplemental Brief on Appeal, pages 8-9.

That argument is not found to be convincing for the reasons already discussed supra. Noctor does not relate to any enzyme that is upregulated upon exposure to heavy metal, but teaches that a poplar plant, which was transformed with the same construct used in the instant specification and demonstrated by Arisi to overexpress glutamylcysteine synthetase, does not result in a plant that provides enhanced heavy metal accumulation as compared with a corresponding wild type plant. Thus, Noctor does have bearing on substituting one plant for another.

Finally, appellants argue that the experimentation required to substitute one plant for another compares favorably with the experimentation that was not found to be undue by the Court of Appeals for the Federal Circuit in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Specifically, appellants argue that practicing the methods of the instant invention "is minor compared with the permitted experimentation under Wands," and that the vast majority of Wands efforts to produce the claimed antibodies fail. Supplemental Brief on Appeal, page 9. Finally, appellants contend, it is not the function of the claims to exclude possible inoperative embodiments. See id.

We agree with appellants that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404. But, "[t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." Id. at 737, 738. In this case, the art demonstrates that a hybrid poplar plant transformed with the same construct used by appellants, wherein the poplar plant was shown to overexpress glutamylcysteine synthetase, failed to hyperaccumulate heavy metals when compared to a corresponding wild type plant. The specification, however, provides only a single example that is supported by a description of the methodology used, as well as supporting data, of a Brassica plant that demonstrates heavy metal accumulation. Thus it would require an undue amount of experimentation to produce hyperaccumulating plants other than Brassica plants without further guidance from applicants as to why the construct produced a hyperaccumulating Brassica plant but failed to produce a hyperaccumulating poplar.

We also agree with appellants that a claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph. See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976), In re Cook, 439 F.2d 730, 732, 169 USPQ 298, 300 (CCPA 1971). But as noted by the court in In re Cook, 439 F.2d

730, 169 USPQ 298 (CCPA 1971), the skilled artisan must be able to determine, without an undue amount of experimentation, those embodiments that would be inoperable. Id. at 735, 169 USPQ at 302 ("[I]t seems to be conceded that a person skilled in the relevant art could determine which conceived but not-yet-fabricated embodiments would be inoperative with expenditure of no more effort than is normally required of a lens designer checking out a proposed set of parameters."); see also Angstadt, 537 F.2d at 504, 190 USPQ at 219 ("Without undue experimentation . . . the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them."). But, as has already been discussed above, we are unable to determine from appellants specification how the poplars presented in Table 2 differ from the poplars produced by Arisi. It would therefore require an undue amount of experimentation to determine other plants that would provide enhanced heavy metal accumulation as compared with a corresponding wild type plant without further guidance from appellants.

CONCLUSION

For the reasons set forth above, the enablment rejection made under 35 U.S.C. § 112, first paragraph, is reversed as to claim 3, but affirmed as to claims 1, 2, 5-8, 13-15, 19-20 and 22.

AFFIRMED-IN-PART; REVERSED-IN-PART

William F. Smith
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Lora M. Green
Administrative Patent Judge

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